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Effect of a combined oral contraceptive containing 3 mg of drospirenone and 30 μg of ethinyl estradiol on the human endometrium

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Objective: To provide an in-depth assessment of the effects of the combined oral contraceptive containing 30 μg of ethinyl estradiol and 3 mg of drospirenone (Yasmin, Schering AG, Berlin) on the endometrium by means of endometrial morphometry in comparison to an untreated cycle.

Design: The open, multicenter study consisted of one untreated precycle and 13 treatment cycles.

Setting: Four gynecologic clinics in Belgium, The Netherlands, and Switzerland were involved.

Patient(s): Forty women with a history of regular menstrual cycles.

Intervention(s): Before the commencement of the trial, 3 months without any hormonal intake was obligatory. The first endometrial sample was done in the untreated precycle, adjusted to the day of LH peak plus 5 to 6 days. During the medication phase, endometrial samples were taken at cycle 3, 6 and 13.

Main Outcome Measure(s): Primary outcome measure of the study was the morphologic assessment of the endometrium with measures such as glandular diameter, glandular epithelial height, and number of vacuolated cells per 1,000 glandular cells. Furthermore, the endometrial thickness was measured by ultrasound.

Result(s): After 13 cycles of medication use the endometrium had an atrophic appearance in 63% of the subjects. The size of the glands, the glandular epithelial height, and the number of glands per square millimeter were already significantly reduced after 3 months' use. Histological and ultrasonographical evaluation of the endometrium indicated a suppression of the proliferative activity of the endometrium.

Conclusion(s): The combination of 30 μg of ethinyl estradiol with 3 mg of drospirenone induces changes of the endometrium that are comparable with other combined oral contraceptives and exhibits a marked antiproliferative effect on the endometrium. The medication was proven to be an effective oral contraceptive and revealed good cycle control characteristics. (Fertil Steril® 2001;76:102–7. ©2001 by American Society for Reproductive Medicine.)

Key Words: Combined oral contraceptive, drospirenone, endometrium

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The novel progestin drospirenone (DRSP), chemically a 17-α-spirolactone derivative, was characterized in receptor-binding studies and in transactivation assays as a progestogen with antimineralocorticoid and antiandrogenic activity and was found to be devoid of any androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity (1). These in vitro findings were in accordance with the pharmacological profile found by in vivo studies in various animal models (2). These characteristics place DRSP in close resemblance to the natural hormone progesterone, which also exerts antimineralocorticoid effects in humans (3, 4). DRSP given in a dosage of 2 mg inhibits ovulation in normally cycling women and has shown to increase sodium excretion when compared with placebo. This mild natriuretic effect of DRSP is expected to be of potential benefit in terms of prevention of sodium retention and rise in blood pressure in susceptible women under combined oral contraceptive (COC) medication (5, 6). The antiandrogenic activity of DRSP is due to a functional blockade of the androgen receptor, and the potency in vivo in the rat was found to be one-third that of cypro-

terone acetate (2). Both the antimineralocorticoid and antiandrogenic effects of DRSP made it a promising candidate for further drug development as progestogenic agent for oral contraception and hormone replacement therapy.

The progestogenic activity of DRSP was evaluated in a variety of animal models, and the results obtained suggest a relative progestational potency of the same order as that of norethisterone acetate (2). The borderline ovulation inhibition dose in women was found to be 2 mg and the combination of 30 μg of ethinyl estradiol (EE) and 3 mg of DRSP did enter into the clinical development of the COC (7). In addition to ovulation inhibition, the contraceptive effect by oral contraceptives are attained by induced changes of the endometrium hampering ovum implantation. The administration of a COC produces variable histological pictures, but in general, results in an underdevelopment of endometrial stroma and glands, whereas the effect on the endometrial glands are often more pronounced. The endometrium becomes scanty and contains only few glands with empty and narrow-lined lumina (8). With time of COC intake, the height of the epithelium decreases, the glands become atrophic, pseudodezidualisation of the stroma can be detected, and, moreover, the development of the spiral arteries does not take place to the same extent as in a normal menstrual cycle (9).

These induced changes in the endometrium are considered to avoid hyperplasia and to minimize the long-term risk for endometrial cancer and could also lead to less menstrual bleeding. In the study reported here, the degree to which the DRSP-containing oral contraceptive affects the endometrium in healthy women was investigated; it was aimed at assessing the effects of the combined oral contraceptive containing 30 μg of EE and 3 mg of DRSP on the endometrium by means of endometrial morphometry in comparison to an untreated cycle. Evaluation of the effect of the study medication on the endometrium characterizes the progestational potency of DRSP, and the results were compared to already existing data on endometrial changes with other combined oral contraceptives. Finally, the gathered data adds valuable information to the safety evaluation of this new drug.

MATERIALS AND METHODS

Subjects

Forty apparently healthy women with a history of regular menstrual cycles volunteered for the study. None of them had used steroidal contraceptives or an intrauterine device during the previous 3 months, and none had had an abortion within the last 6 months or delivery within 1 year before admission to the study.

The medical ethics committee of each of the study sites (Geneva, Switzerland; Leiden, The Netherlands; Liège and Nijmegen, Belgium) approved the study, and each woman gave her written consent before enrollment. The study was performed with the regulations and recommendation of the Declaration of Helsinki (Hong Kong 1989).

Episodes of bleeding and any adverse events were recorded throughout the trial.

TABLE 1

Baseline characteristics of age, height, weight, age at menarche and intracyclic bleeding before the start of the trial.

	Subjects		
	n	Mean	Standard deviation
Age (yr)	40	27.6	5.0
Height (cm)	40	169.5	6.4
Weight (kg)	40	64.7	10.3
Age at menarche (yr)	40	12.9	1.7

Note: Data given as mean ± standard deviation.

Lüdicke. Combined oral contraceptive and human endometrium. Fertil Steril 2001.

Trial Plan

The women who volunteered for the study were assigned randomly to two independent groups. In group A, the treatment effects were investigated after 3 and 13 treatment cycles. In group B, the treatment effects were investigated after 6 and 13 treatment cycles. Both groups received the same medication, thus the only difference between the two assessment groups was the timing of the endometrial biopsies.

The study consisted of one untreated precycle and 13 treatment cycles. Before the commencement of the trial, a minimum of 3 months without any hormonal intake was obligatory. The first endometrial sample in the untreated precycle was performed adjusted to the day of LH peak plus 5 to 6 days. A home monitoring kit to detect the LH peak in urine (OvuQuick, Quidel, San Diego, CA) was used for this purpose. Baseline characteristics for all 40 subjects are summarized in Table 1.

Test Material

The study medication consisted of 21 film-coated tablets of 30 μg of ethinyl estradiol and 3 mg of drospirenone per blister pack. One tablet was taken daily for 21 days, followed by 7 tablet-free days.

Endometrial Samples and Morphometric Analyses

The endometrial sample was performed with a Pipelle de cornier device without dilatation of the cervix and without anesthesia. The endometrial strips (10–15 mm) were immediately fixed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. In addition to a general histologic assessment of the endometrial biopsies, numeric data

TABLE 2

Morphological indices applied for the trial.

Parameter	Unit
Number of glands	/mm^2
Diameter of glands	μm
Glandular epithelial height	μm
Number of vacuolated cells	/1,000 glandular cells
Mitoses glands	/1,000 glandular cells
Pseudostratification	Score[a]
Predecidualization	Score[a]

[a] Score 0–3; 0 = none, 1 = slight, 2 = moderate, and 3 = marked.

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was generated on morphometric parameters of the endometrium so as to obtain quantitative information about the endometrial morphology. The indices examined are shown in Table 2.

Ultrasound Examination of the Endometrium

At each study visit, a transvaginal sonographical examination of the endometrium was done with the use of high frequency (5–7 MHz) transducers. Endometrial thickness was measured as the distance between both endometrial/myometrial borders.

Statistical Analysis

The primary target variables were the individual changes from baseline (precycle) to the 3rd, 6th, and 13th treatment cycle of the diameter of glands, the height of the glandular epithelium, and the number of vacuolated glandular cells. All other morphological indices variables were considered secondary target variables (Table 2).

The two-sided 95% confidence intervals were computed under the assumption of normal deviates for all variables except to the score variables pseudostratification and predecidualization.

Intention-to-Treat and Valid Case Analyses

Two types of analyses were done: a valid-case (VCA) analysis for the primary outcome measures and an intention-to-treat (ITT) analysis on all variables in addition to the VCA.

A subject was reckoned as a valid case if she had no protocol deviation that might have affected the primary outcome measures of the trial, meaning the morphologic assessment of the endometrium. According to the study protocol, the following criteria had to be fulfilled: at least one biopsy at baseline and at the end of the study had to be existent, not more than four missed pills in each medication cycle were allowed, and the months without hormonal medication before the trial had to be adhered to. In contrary, the only prerequisite for a subject to be included into the ITT analysis was that she had taken at least one pill. No notable difference was seen concerning the histologic assessment between VCA and ITT population. No endometrial pathology was detected in the ITT nor in the VCA population. For the morphometric parameters, the VCA is reported only.

RESULTS

Disposition of Study Subjects

After having given informed consent, 40 women were assigned to two different groups according to a list reflecting the different time points of the intermediate biopsy, 19 subjects to group A (intermediate biopsy cycle 3) and 21 subjects to group B (intermediate biopsy cycle 6). Two women initially assigned to group A were erroneously switched to group B before the their first intermediate biopsy, so that they were evaluated in group B; thus, a total of 40 subjects were included in the ITT analysis: 17 were evaluated in group A and 23 in group B. Intermenstrual bleeding characteristics and adverse events during the course of the study were evaluated by the ITT analysis.

Seven women discontinued the trial prematurely, in six women, the endometrial biopsy at baseline or in treatment cycle 13 was not available or yielded not sufficient material, and one woman was excluded from the analysis because she switched accidentally to a different COC; therefore, 26 cases entered into the valid case analysis, 13 subjects in each group. Some of the biopsies during treatment resulted in too few material for morphometric evaluation, thus, at cycle three, 11 biopsies, and at cycle six, 10 biopsies, were evaluable, respectively.

Intermenstrual Bleeding

Bleeding that occurred outside the tablet-free interval was described as intermenstrual bleeding, presenting either as scanty bleeding (spotting) or with the strength of a menstrual period (breakthrough bleeding). Thirteen women reported spotting in the first treatment cycle. The incidence of spotting declined continuously afterwards. Nineteen subjects reported intermenstrual bleeding at least once from the second to the 13th cycle. One woman reported an episode of breakthrough bleeding during the treatment period. No correlation between episodes of intermenstrual bleeding and the morphometric assessment of the endometrium was detected.

Adverse Events

Three women discontinued the trial because of the following adverse events: acne, headache, and weight gain. The most frequently mentioned complaints during drug intake were headache (eight cases), breast tension (five cases), and nausea (four cases).

Morphometry

According to the collected tissue samples at baseline, all 26 women showed a histologically secretory endometrium, which contained glands in which the epithelial cells exhibited sub- or supranuclear vacuolization or showed apocrine-

TABLE 3

Indices of endometrial morphology before (pre-cycle) and during administration of 3 mg of DRSP and 30 μg of EE.

Endometrial indices	Pre-cyle (n = 26)	Cycle 3 (n = 11)	Cycle 6 (n = 10)	Cycle 13 (n = 26)
Number of glands/mm^2	20.5 ± 8.3	9.9 ± 3.9 (−10.3 ± 10.1) [−3.3; −17.2]	10.1 ± 9.3 (−11.6 ± 10.0) [−4.5; −18.7]	10.8 ± 5.5 (−9.7 ± 9.4) [−5.9; −13.5]
Diameter of glands (μm)	35.8 ± 16.4	22.3 ± 10.1 (−8.6 ± 17.7) [−19.1; 1.9]	20.6 ± 7.6 (−18.8 ± 17.8) [−29.9; −7.7]	15.8 ± 4.8 (−20 ± 18.1) [−26.1; −14]
Glands epithelial height (μm)	20.3 ± 4.6	11.1 ± 2.6 (−9.6 ± 6.5) [−13.5; −5.8]	11.8 ± 4.7 (−9.8 ± 3.7) [−12.1; −7.4]	10.6 ± 2 (−9.7 ± 5.2) [−11.6; −7.9]
Number of vacuolated cells/ 1,000 glandular cells	376.5 ± 342	0	0	0
Mitoses of glands/1,000 cells	0.3	0	0	0

Note: Data given as mean ± SD; (mean absolute change from pre-cycle ± SD); [Confidence interval for mean change from pre-cycle].

Lüdicke. Combined oral contraceptive and human endometrium. Fertil Steril 2001.

type secretion into the gland lumina. During treatment, an increasing atrophy of the endometrium was found, as characterized by small glands with a single layer of inactive epithelium, without mitotic figures or secretory activity, and no evidence of decidual changes. The endometrium appeared to be atrophic in 41% and 44% of women having used the medication for 3 and 6 cycles, respectively. After 13 cycles of COC use, atrophy was described in 63% of the cases.

Table 3 summarizes the different morphometric indices and their change from baseline during the study period. A distinct suppression of proliferative activity of the functional layer of the endometrium was reflected by the reduced size of the glandular diameter compared with baseline during treatment. This effect was already seen after three cycles of COC intake and was even more pronounced and statistically significant at treatment cycle 6 and 13. Equally, a reduction of the number of glands and the gland's epithelial height was found to be reduced when compared with baseline. A significant decrease in epithelial height was already observed at 3 months of medication and remained in the same range at treatment cycle 6 and 13 (Table 3). The number of vacuolated cells per 1,000 glandular cells was suppressed to zero under treatment from a mean baseline value of 376 vacuolated cells. At the baseline biopsy in one case, "slight predecidualization" was scored. During treatment, two histologies were reported with signs of slight predecidualization, two cases with moderate predecidualization, and one case with marked predecidualization. Except in one case, no pseudostratification was seen under treatment.

Finally, the ultrasonographic measurements of the endometrium correlated well with the results of the morphometric measurements and indicated a suppression of the endometrium. The full sonographic reduction of endometrial thickness was reached after six cycles (Table 4).

DISCUSSION

Throughout the normal menstrual cycle, the morphologic variation of the endometrium has been documented, and some of the major features of these changes that are also represented in the morphometric indices applied for this study are schematically shown in Figure 1.

The number of glands per square millimeter is approximately 20 and does not change significantly during the normal menstrual cycle, whereas the glandular diameter

TABLE 4

Endometrial thickness (mm) as assessed by ultrasound—mean values and absolute changes.

Cycle	Subjects	Mean value	Standard deviation	Mean absolute change from baseline	Standard deviation
pre-cycle	26	7.5	2.8		
cycle 3	26	4.8	1.9	−3.7	2.7
cycle 6	26	3.7	1.5	−4.8	2.3
cycle 13	26	3.9	3.0	−4.6	3.6

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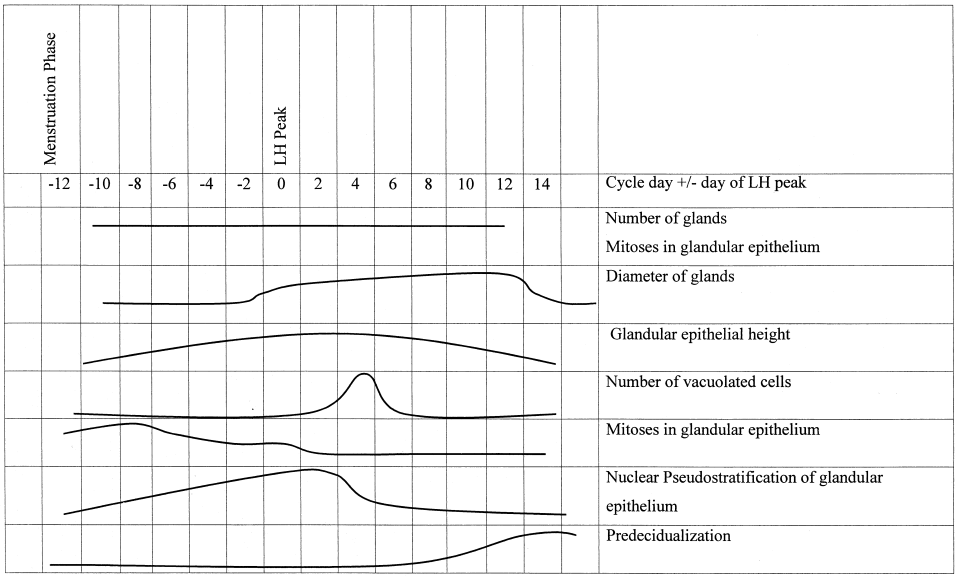
FIGURE 1

Selected endometrial morphologic changes during the menstrual cycle.



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shows a linear increase from day LH-1 to day LH+11/+12. From day LH+6, glycoprotein-rich cytoplasmatic products are expelled into the glandular lumen, and the peak of intraglandular secretions coincides with the time of implantation of the free blastocyst (day 7 after ovulation) if fertilization takes place (10). The glandular epithelial cells are characterized by rapid growth and increasing epithelial height from LH-11 through LH+2, and the first reliable histologic alteration that is considered specific to ovulation is basal vacuoles that start to appear in the glandular epithelium on day LH 0, and their number increases steadily up to day LH+4 (11). The preovulatory endometrium is characterized by proliferation of glandular cells, stromal cells, and vascular endothelial cells, and the maximum number of endometrial cells engaged in DNA synthesis is seen between cycle day 8 and 10 and corresponds to maximal mitotic activity, peak plasma estradiol levels, and maximum concentration of estrogen receptors (10). The size of the glands does not keep pace with this glandular growth, and the tall columnar epithelial cells finally pile up against each other with their nuclei at different levels, giving rise to pseudostratification (12). Predecidualization starts to take place around day LH+8 and is characterized by the conversion of stromal cells into plump epithelial-like cells with enlarged nuclei and increased cytoplasm. The cells have metabolic functions related to pregnancy or, if conception has not occurred, to the menstrual breakdown of the endometrium by phagocytotic digestion of extracellular collagen matrix (13).

Distinct histological changes can be observed during the intake of combined contraceptive steroids in the endometrium. Its glandular component is a sensible indicator for measuring the effect of contraceptive steroids. The progestin component in the COC inhibits proliferation of the endometrium, which is in line with our findings in which signs of proliferation such as mitoses, size of the glands, pseudostratification, and epithelial height were found to be clearly surpressed. When given at a dose of 30 μg of EE, in combination with 3 mg of DRSP, atrophic appearance of the endometrium was found in 44% of the women at six treatment cycles and in 63% of the women at 13 treatment cycles. These results are similar to what has been reported for other COCs, such as the combination of 75 μg of gestodene with 20 μg of EE in which the rate of atrophy was about 50% at 6 months of treatment (14). The reduction of the number of glands as seen in our study and others is a phenoma that cannot be observed in the menstrual cycle without COC medication and is apparently progestin-dose dependent. It has been shown that the release of 50 μg of norethisterone per 24 hours via a vaginal ring did not reduce the number of glands, whereas the release of 200 μg/24 hours diminished significantly their number after 10 weeks of application (15). In view of the fact that the induced endometrial changes are limited to the functionalis layer of the endometrium but do not affect the basalis layer, this effect is known to be reversible after withdrawal of the contraceptive steroids (8).

Although histology and morphometric measurements allow for the assessment of the impact of contraceptive steroids on the endometrium when compared with the normal

cycle, give insights in the progestogenic potency of certain progestins, and provide common grounds for the comparison of endometrial effects of different COCs, they do not predict intermenstrual bleeding. Like earlier reports, the present study did not reveal any correlation between the number of days of intermenstrual bleeding and the morphometric assessment of the endometrium. After all, it is still the empirical data collected in a substantial number of women that will provide the necessary information on cycle control. Cycle control with both 30 μg of EE/3 mg of DRSP and 30 μg of EE/150 μg of desogestrel (Marvelon) was evaluated in two randomized, open-label studies of 13 and 26 treatment cycles, respectively. Taken together, data were generated for 29,376 cycles in the DRSP group and 14,850 cycles in the Marvelon group. Cycle control with both preparations was shown to be very good. A total of 8% in the DRSP group and 7% in the Marvelon group had had intermenstrual bleeding during the 6 months before the start of the study, a reported incidence that was similar to the rate of occurrence during the treatment phase (16, 17).

Depending upon dosage and type of progestin, predecidual changes of the stroma take place and strong predecidual reaction was found in the stroma using high doses of the 19-norsteroid norethynodrel (18). In preparations where the 19-norsteroid was reduced, considerably less decidual reaction was found (19), whereas 35 μg of EE in combination with norgestimate (0.25 mg) yielded no decidual response, nor did the combination of 50 μg of EE and 2 mg of cyproterone acetate (CPA) (9). In this study, the overall rate of decidual reaction under treatment was found to be 19% what is in the range that has been reported for the combination of 20 μg of EE with 75 μg of gestodene. Taking together the key information that might summarize the progestogenic potency of a progestin on the endometrium-like antiproliferative activity, atrophic changes, and predecidualization, it seems, according to our results, that 3 mg of DRSP exhibits strong progestational effects on the human endometrium.

In conclusion, the combined oral contraceptive containing 30 μg of EE and 3 mg of drospirenone shows good suppression of endometrial activity, and the histological markers for antiproliferative activity and induced atrophic changes compare well to other modern low-dose combined contraceptives. The overall tolerance was found to be good and, in large-scale trials, good cycle control was confirmed.

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